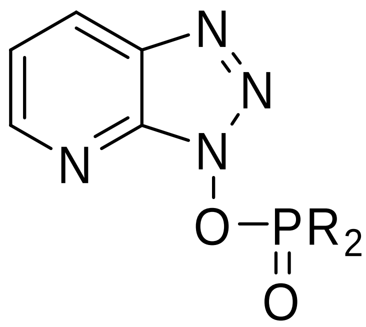
Organophosphorus Esters of 1-Hydroxy-7-azabenzotriazole: A New Peptide Couping Reagent

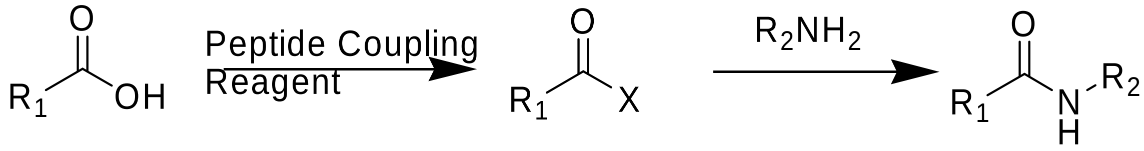


J. Org. Chem. **2004**, *69*, 62-71

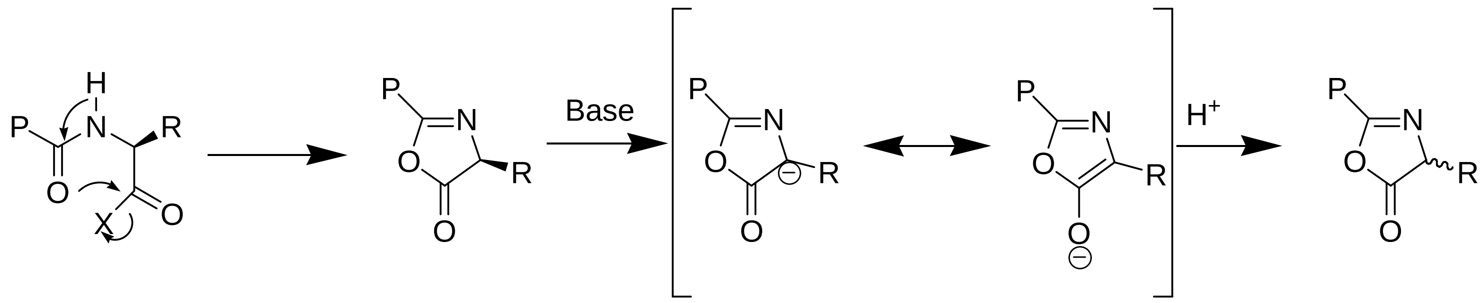
Louis A. Carpino, Jusong Xia, Chongwu Zhang, and Ayman El-Faham

Current Literature
Chenbo Wang @ Wipf Group
June 23, 2005

Peptide Coupling: General Scheme

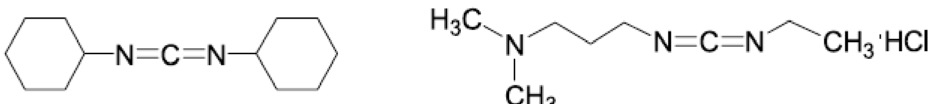


Major racemization pathway:

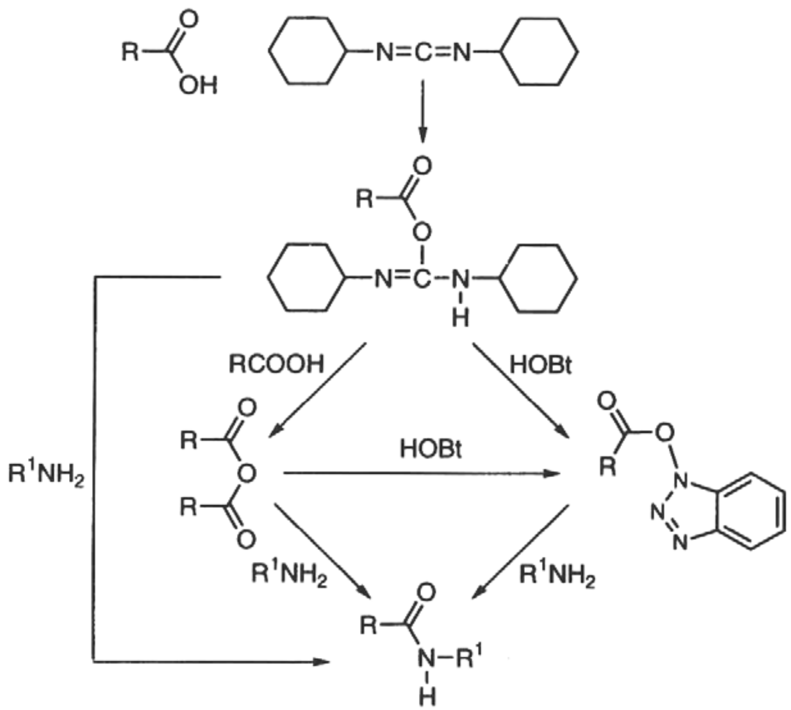


Han, S.-Y. Kim, Y.-A., *Tetrahedron* **2004,** *60,* 2447–2467

Couping Reagents:
1. Carbodiimdes



DCC EDC

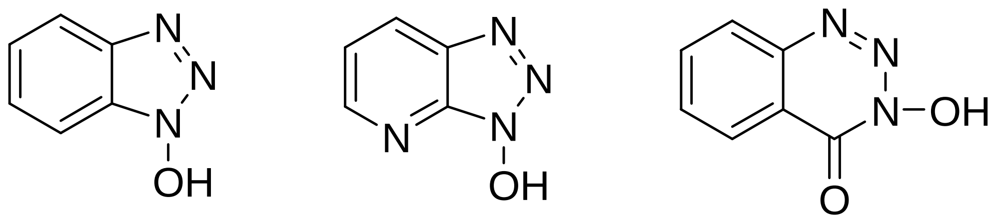


- Cheaply available
- Moderate activity
- Low racemization if combined with additives

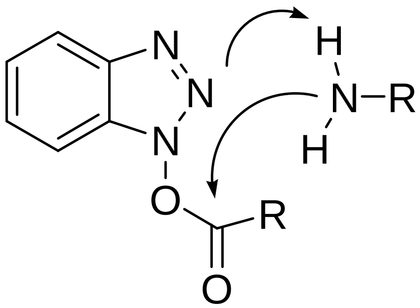
Williams, P. L., Albericio, F., Giralt, E., *"Chemical Approaches to the Synthesis of Peptides and Proteins"*, CRC Press 1997

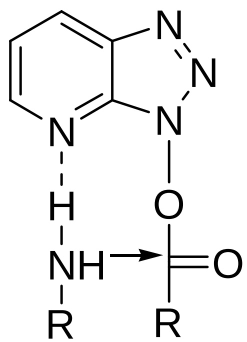
1. Carbodiimdes (cont.): Additives

- Function: suppressing racemization, improving yield



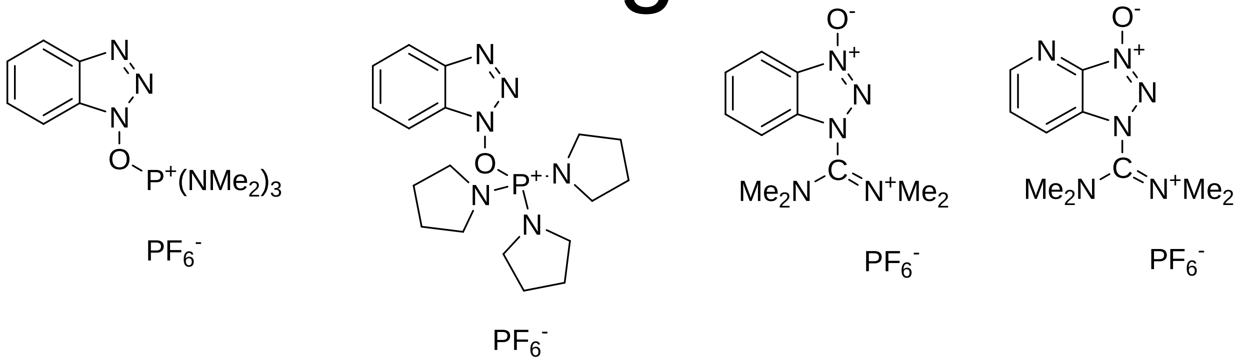
HOBt HOAt HODhbt



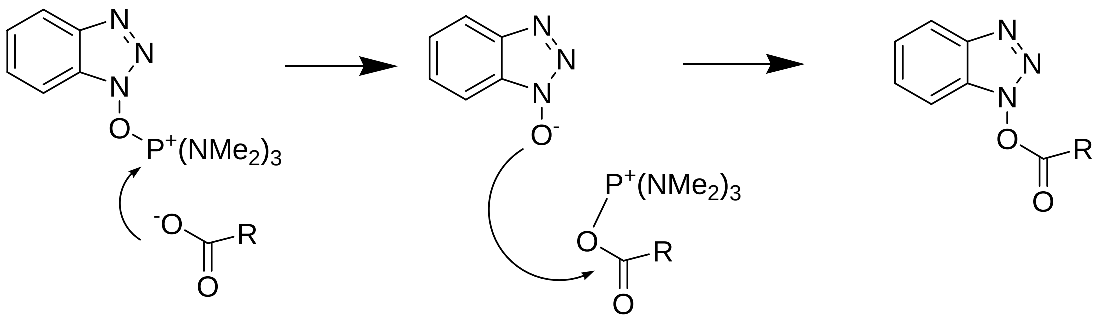


Williams, P. L., Albericio, F., Giralt, E., *“Chemical Approaches to the Synthesis of Peptides and Proteins”*, CRC Press 1997

2. Phosphonium and Uronium Reagents



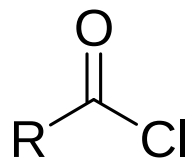
BOP PyBOP HBTU HATU

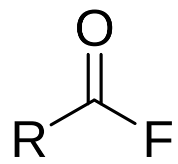


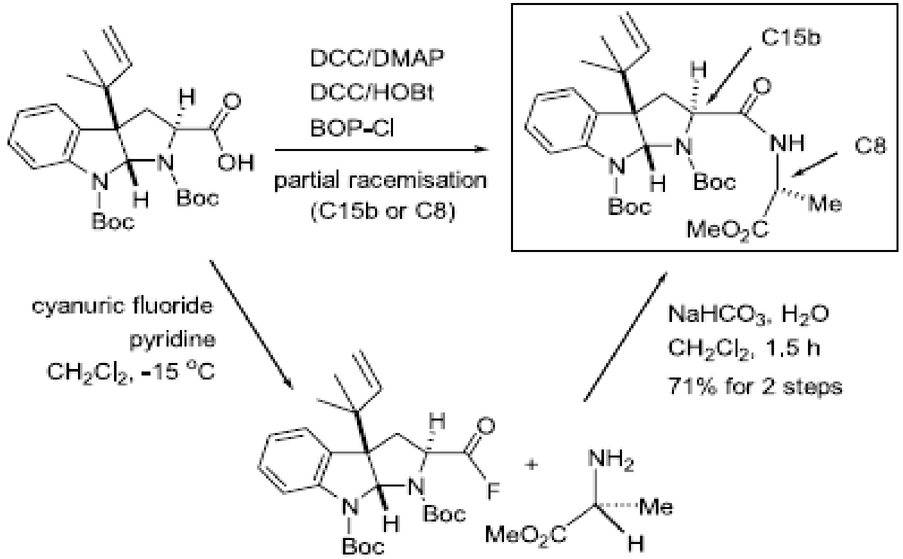
- Higher activity
- Lower racemization

Williams, P. L., Albericio, F., Giralt, E., *"Chemical Approaches to the Synthesis of Peptides and Proteins"***,** CRC Press 1997

3. Acyl Halides





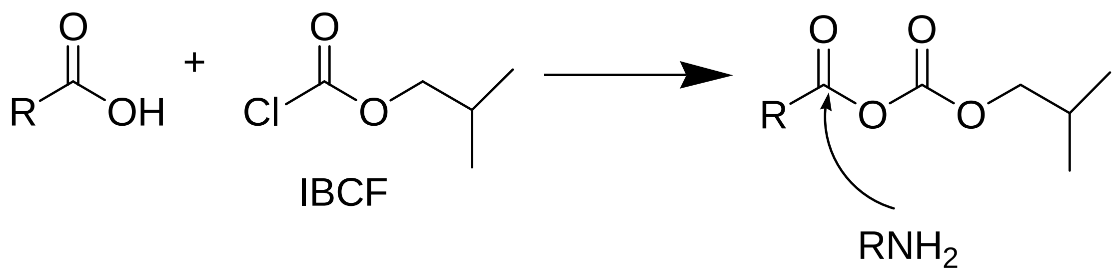


- Highest activity
- Extensive racemization
- Harsh conditions required for the formation of acyl chlorides

Williams, P. L., Albericio, F., Giralt, E., *“Chemical Approaches to the Synthesis of Peptides and Proteins”,* CRC Press 1997

Depew, K. M., Marsden, S. P., Zatorska, D.; Zatorski, A., Bornmann, W. G., Danishefsky, *J. Am. Chem. Soc.* 1999, **121**, 11953–11963.

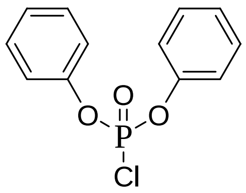
4. Mixed Acid Anhydrides



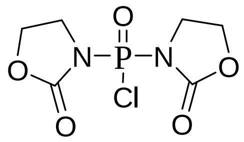
- Clean reaction
- Mild condition
- Cheap

Williams, P. L., Albericio, F., Giralt, E., *"Chemical Approaches to the Synthesis of Peptides and Proteins"*, CRC Press 1997

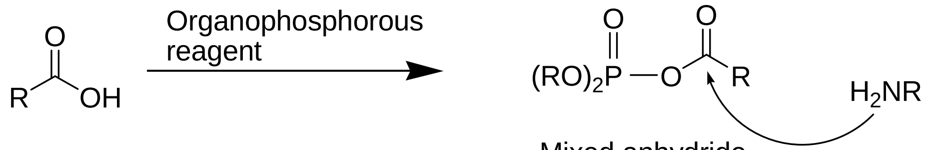
5. Organophosphorous Reagents



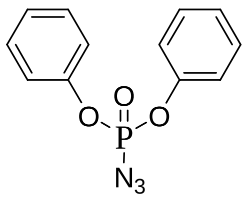
DPP-Cl



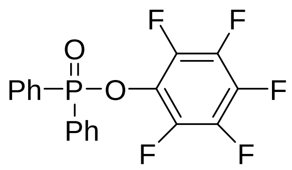
BOP-Cl



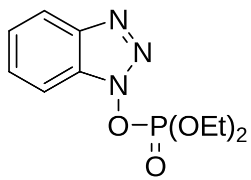
Mixed anhydride



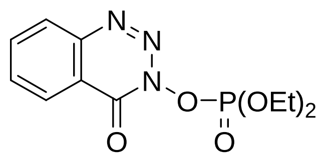
DPPA



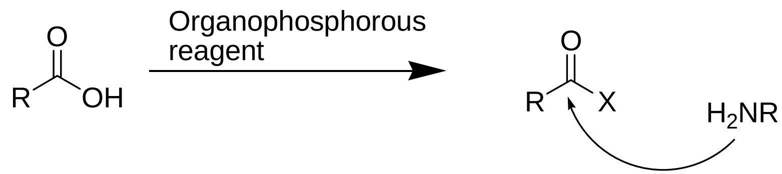
FDPP



DepObt



DepODhbt

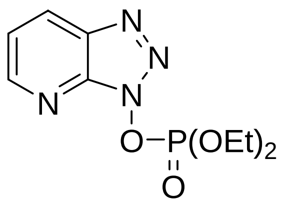


Active ester

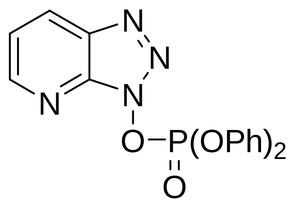
- DPPA, FDPP: Mildly active
- DepObt, DepODhbt: Lowest racemization

Han, S.-Y. Kim, Y.-A., *Tetrahedron* **2004,** *60,* 2447–2467

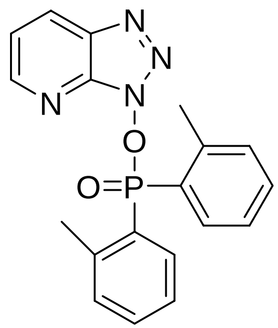
Design and Synthesis of New Coupling Reagents



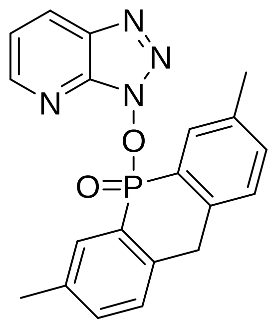
DepOAt (unstable)



DpopOAt (unstable)



DtpOAt



DmppOAt

Carpino, L. A., Xia, X., Zhang, C., El-Faham, A., *J. Org. Chem.* 2004, **69**, 62-71

Active Ester Formation

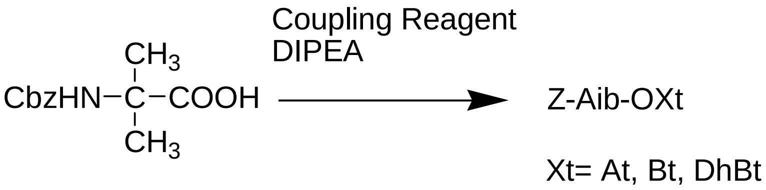
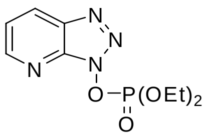


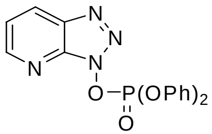
TABLE 1. Approximate Halftimes for the Formation of Z-Aib-OXt

coupling reagent	$t_{1/2}$ (DMF) (min)	$t_{1/2}$ ($CDCl_3$) (min)
DepOAt, 9	<2	2−3
DpopOAt, 10	<2	2−3
DepODhbt, 2	7−8	45−47
DpopODhbt[a]	<2	<2
DtpOBt, 16	65−70	11−12 h
HATU[a]	<2	14−15
HAPyU[a]	<2	<2
HDTU[a]	<2	<2
HBTU[a]	<2	>24 h

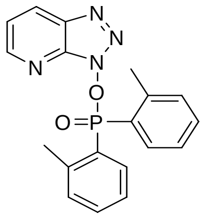
[a] See list of abbreviations not defined in text.



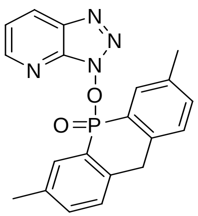
DepOAt (unstable)



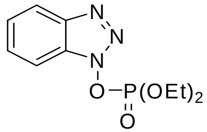
DpopOAt (unstable)



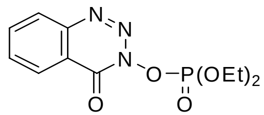
DtpOAt



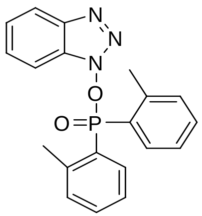
DmppOAt



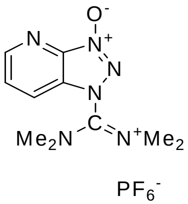
DepObt



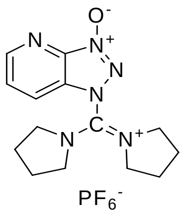
DepODhbt



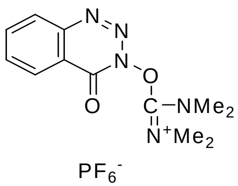
DtpOBt



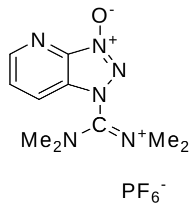
HATU



HAPyU



HDTU



HATU

Extent of Epimerization

Z-Phe-Val¦Pro-NH_2 Z-Gly-Phe¦Pro-NH_2 Z-Gly-Gly-Val¦Ala-Gly-Gly-OMe

TABLE 2. Effect of Coupling Reagent on Extent of Epimerization during [2 + 1] Coupling Leading to Z-FVP-NH_2 and Z-GFP-NH_2 and [3 + 3] Coupling Leading to Z-GGVAGG-OMe in DMF with 2 equiv of TMP as Base[a,b]

coupling reagent	Z-FVP-NH_2	Z-GFP-NH_2	Z-GGVAGG-OMe
DepOAt, **9**	0.9 (0.9)	<0.1	<0.1
DmppOAt, **15**	3.6 (2.0)	0.3	
DtpOAt, **14**	2.9 (1.4)	0.4	
HATU[c]	5.0 (1.8)	1.1 (0.9)	2.4
DepODhbt, **2**	3.5	0.3	2.4
DtpODhbt, **17**	4.3 (3.6)		
HDTU[c]	8.5 (4.0)		3.3
DtpOBt, **16**	11.4	2.2	
HBTU[c]	14.2	3.6	8.2

[a] All figures are given as percent of the LDL- or DL-form as observed by HPLC analysis. [b] Figures in parentheses refer to identical runs but with 1 equiv of the appropriate HOXt added. [c] See list of abbreviations not defined in text.

Application On Solid Phase Peptide Synthesis (SPPS)

- ACP: Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2

TABLE 3. Distribution of Products, Including Various Deletion Peptides, According to HPLC Analysis[a] for the Assembly of ACP (65−74) via HOAt-Derived and Related Coupling Reagents

entry	coupling method	equiv of reagents[b]	preactivation time (min)	coupling (min)	ACP (%)	−2Ile (%)	$-Ile^{72}$ (%)	$-Ile^{69}$ (%)	−Val (%)	−Ala (%)	−Asn (%)
→ 1	DepOAt, 9	1.5	7	1.5	84		2	2	1	4	5
→ 2	DpopOAt, 10	1.5	7	1.5	85		2	1	2	6	3
3	DepODhbt, 2	1.5	7	1.5	6	9	13	19	3		1
4	DpopOBt[c]	1.5	7	1.5	23	21	26	19	1	1	2
5	HATU[c]	1.5	7	1.5	85		1	1	3		10
6	HDTU[c]	1.5	7	1.5	38	15	15	26			5
→ 7	DepOAt, 9	1.5	0	1.5	86		4	2	2	3	1
→ 8	DpopOAt, 10	1.5	0	1.5	81		4	1	1	7	
9	DepODhbt, 2	1.5	0	1.5	< 1[d]						
10	DpopOBt[c]	1.5	0	1.5	29	17	25	17	2		3
11	HATU[c]	1.5	0	1.5	87		3	1	2		6
12	HDTU[c]	1.5	0	1.5	30	15	19	22	3		4

[a] A reversed-phase C-18 column was used with elution by a linear gradient over 20 min of 0.1% TFA in MeCN and 0.1% TFA from 1:19 to 1:1, flow rate 1.0 mL/min. [b] Couplings were carried out in DMF in the presence of 2 equiv of DIEA per equivalent of Fmoc-amino acid/coupling reagent. [c] See list of abbreviations not defined in text. [d] Only a trace of the desired product was obtained.

Conclusion

- Conclusion:
  - A new class of organophosphorous coupling reagent based on HOAt was made, which showed high activity with low epimerization level.
- Future Work:
  - More extensive testing of the new reagent
  - Stability of the reagent